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REVIEW

Artemisinin and artemisinin derivatives as anti-fibrotic therapeutics

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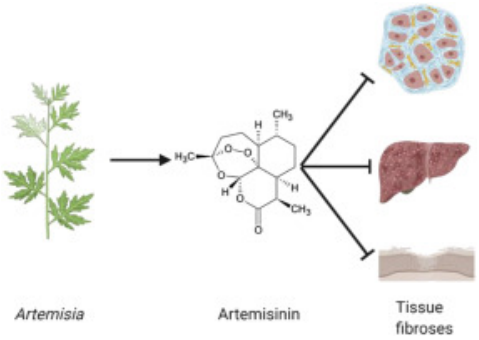
Abstract

Fibrosis is a pathological reparative process that can occur in most organs and is responsible for nearly half of deaths in the developed world. Despite considerable research, few therapies have proven effective and been approved clinically for treatment of fibrosis. Artemisinin compounds are best known as antimalarial therapeutics, but they also demonstrate antiparasitic, antibacterial, anticancer, and anti-fibrotic effects. Here we summarize literature describing anti-fibrotic effects of artemisinin compounds in *in vivo* and *in vitro* models of tissue fibrosis, and we describe the likely mechanisms by which artemisinin compounds appear to inhibit cellular and tissue processes that lead to fibrosis. To consider alternative routes of administration of artemisinin for treatment of internal organ fibrosis, we also discuss the potential for more direct oral delivery of *Artemisia* plant material to enhance bioavailability and efficacy of artemisinin compared to administration of purified artemisinin drugs at comparable doses. It is our hope that greater understanding of the broad anti-fibrotic effects of artemisinin drugs will enable and promote their use as therapeutics for treatment of fibrotic diseases.

Graphical abstract

Artemisinin drugs, isolated from *Artemisia*, effectively prevent or treat multiple types of tissue fibrosis when administered to several preclinical animal models of varied etiologies.



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KEY WORDS

Fibrosis; *Artemisia*; Artemisinin; Artesunate; Fibroblast; Myofibroblast; Scar; TGF-β

Abbreviations

α-SMA, smooth muscle α-actin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMPK, AMP-activated protein kinase; ASP, aspartate aminotransferase; BAD, BCL-2-associated agonist of cell death; BDL, bile duct ligation; BSA, bovine serum albumin; BUN, blood urea nitrogen; CCl_4, carbon tetrachloride; Col I, type I collagen; CTGF, connective tissue growth factor; DHA, dihydroartemisinin; DLA, dried leaf *Artemisia*; ECM, extracellular matrix; EMT, epithelial-to-mesenchymal transition; FLS, fibroblast-like synoviocyte; HA, hyaluronic acid; HSC, hepatic stellate cell; HUVEC, human umbilical vein endothelial cell; i.p., intraperitoneal; LAP, latency-associated peptide; LDH, lactate dehydrogenase; MAPK, mitogen-activated protein kinase; MI, myocardial infarction; MMP, matrix metalloproteinase; mTOR, mechanistic target of rapamycin; NAG, *N*-acetyl-β-D-glucosaminidase; NICD, Notch intracellular domain; PCNA, proliferating cell nuclear antigen; PHN, passive heymann nephritis; ROS, reactive oxygen species; sCr, serum creatinine; STZ, streptozotocin; TGF, β-transforming growth factor-β; TIMP, tissue inhibitor of metalloproteinase; UUO, unilateral ureteral obstruction

1. Introduction

1.1. Fibrosis

1.1.1. General disease statistics and fibrotic diseases

Fibrosis refers to a pathophysiological tissue process wherein wound healing proceeds *via* a non-regenerative mechanism and leads instead to formation of a scar[1]. Instead of replacement of damaged tissue with its healthy counterpart, constructed with its native cellular constituents and appropriate microstructure, fibrotic tissue is largely acellular and lacks the functional properties of the tissue that it seeks to replace. For a tissue like the skin, limited tissue fibrosis results primarily in minor cosmetic abnormalities and negligible discomfort, though fibrosis manifesting over large surface areas of the skin lead to profound limitations in the ability of the body to regulate temperature

through sweat secretion, critical disability through wound contracture, and socially debilitating cosmetic disfigurement, ultimately leading to high healthcare costs and patient morbidity[2]. In internal organs whose vital functions rely heavily on complex tissue microstructure and active cellular function, fibrotic responses manifesting throughout even limited volumes of tissue can lead to morbidity and mortality through loss of organ function and/or complete organ failure. It is for this reason that nearly half of all mortalities in the developed world are attributed to fibrosis[3].

Each fibrotic disease state contains clinical and basic science challenges and nuances specific to that disease and to the organ within which it manifests. Thus, knowledge of function of an organ and its constituent tissues, as well as an understanding of disease-specific etiology, is critical to furthering treatment and therapy for any specific fibrotic disease. That being said, researchers of the basic science and pathophysiology of fibrosis now recognize that there are critical, reasonably generalizable processes that underlie fibroses of diverse organs, including but not limited to the transforming growth factor beta (TGF-β) family of master fibrosis-regulating cytokines, other signaling pathways and cellular processes, and the paradigm of the pathologically activated myofibroblast[3].

1.1.2. Cellular and molecular processes in fibrosis

Upon loss of tissue homeostasis, tissue-specific myofibroblast progenitor cells will be stimulated by factors in the local environment to differentiate into myofibroblasts. Myofibroblasts are contractile mesenchymal cells characterized by expression and incorporation of smooth muscle alpha-actin (α-SMA) within cytoplasmic actin-myosin stress fibers, which also secrete a large quantity of extracellular matrix proteins including type I collagen (Col I) and extra domain A (ED-A) fibronectin[4]. While myofibroblasts also play key roles in healthy wound healing, as wound contracture and collagen deposition are critical processes occurring in standard wound repair, persistence of myofibroblasts in the wound site long after the proliferative phase has subsided is indicative of formation of a fibrotic tissue scar[5]. The progenitor cells that differentiate in order to become myofibroblasts vary among tissues and among fibrotic disease states, but the paradigm of pro-fibrotic myofibroblasts persisting at the site of wounded tissue and depositing excessive extracellular matrix leading to a non-functional, mechanically aberrant scar is consistent across organs and across fibrotic pathologies[4]. This lends a degree of generality to myofibroblast biology that extends beyond any one organ or disease, meriting further investigation of therapies that prevent or reverse myofibroblast differentiation, or that induce myofibroblast apoptosis, as they may be potentially applicable across multiple fibrotic diseases and tissues.

1.1.2.1. TGF-β signaling

One of the most critical, ubiquitous paradigms underlying fibrosis is that of TGF-β signaling. TGF-β signaling leads to fibrotic phenotypes through several different mechanisms. Most directly, TGF-β differentiates tissue fibroblasts into myofibroblasts[6,7], leading to contraction and deposition of large amounts of extracellular matrix. Other roles of TGF-β in fibrosis include stimulation of the epithelial-to-mesenchymal transition (EMT), enabling derivation of pathological myofibroblasts from other precursor cells in the tissue[8]. Under canonical TGF-β signaling, a pathological stimulus liberates mature TGF-β from its latency-associated peptide (LAP). Mature TGF-β then signals to fibroblasts or other tissue-specific myofibroblast precursor cells by binding the receptor TGF-βRII on the cell surface, which forms a dimer with TGF-βRI. This heterodimer then phosphorylates the C-terminus of SMAD2 and SMAD3, effector proteins that translocate to the nucleus and, along with binding partner SMAD4 and other accessory proteins, bind to SMAD-binding elements in the promoters of pro-fibrotic genes, driving processes such as myofibroblast differentiation, collagen deposition, and collagenase inhibition. TGF-β signaling is also subject to negative regulation, as inhibitory SMAD6 and SMAD7 bind TGF-β receptors and antagonize signal transduction[9]. In addition, TGF-β/TGF-βR can activate, in a SMAD-independent manner, other pathways including mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathways, resulting in cross-talk with other upstream cytokines that also utilize these ubiquitous signaling paradigms, many of which are also critical to processes involved in myofibroblast formation

and tissue fibrosis (Fig. 1)[10].

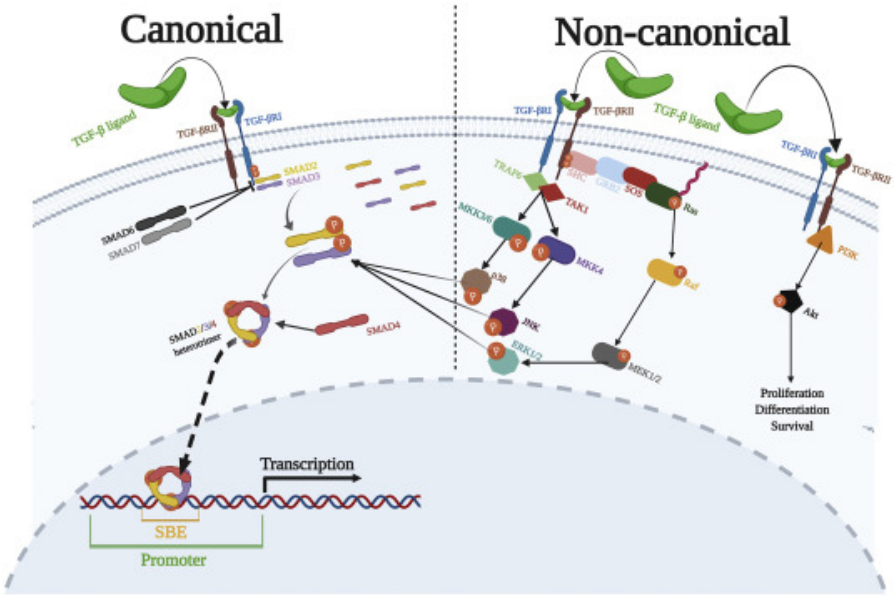

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Figure 1. TGF-β signaling. TGF-β signaling is a major paradigm underlying all manifestations of tissue fibrosis. Under canonical signaling TGF-β ligands are liberated from the extracellular microenvironment, upon which TGF-β binds to its membrane-bound receptor TGF-βRII, resulting in phosphorylation of the co-receptor TGF-βRI and subsequent propagation of the signal. TGF-βRI then phosphorylates serine residues at the C-termini of SMAD2 and SMAD3. Phosphorylated SMAD2/3 residues bind to SMAD4, and the trimeric SMAD complex translocates to the nucleus, where it binds SMAD-binding elements (SBEs) in the promoters of TGF-β-sensitive genes and drives their expression. The inhibitory SMADs (SMAD6 and SMAD7) serve to interfere with the signaling pathway by inhibition of the binding and activation of SMAD2 and SMAD3 by TGF-βRI. Under non-canonical signaling, activation of TGF-βRII/TGF-βRI proceeds, after which other signaling pathways follow. One alternative set of pathways are the MAPK pathways, which lead ultimately to activation of the MAPK proteins ERK, JNK, or p38, which can then modulate canonical TGF-β signaling by phosphorylating the linker domains of SMAD proteins, affecting their subcellular localization and activity. Alternatively, the TGF-β/TGF-βR pathway can lead to activation of PI3K/Akt, resulting in critical effects on cell survival, proliferation, and differentiation, among many others, through downstream molecular pathways including activation of mTOR.

1.1.2.2. Mitogen-activated protein kinase signaling

While TGF-β is rightfully considered the master regulator of tissue fibrosis, its canonical mechanism of signal transduction is far from the only pathway involved in causation and maintenance of fibrotic disease states. Another critical signaling paradigm is that of MAPK signaling. MAPK signaling can be induced by many different stimuli including growth factors, pro-inflammatory cytokines, reactive oxygen species, and osmotic stress[11]. Broadly, the typical MAPK paradigm, which is well-conserved throughout eukaryotes, consists of three “layers” of kinases that phosphorylate each other step-wise; the MAPKKKs phosphorylate the MAPKKs, which phosphorylate the MAPKs, which proceed to phosphorylate their target proteins, modulating gene expression and cell behavior[12]. Though the basic outline of these pathways is conserved, the effects of activation of these pathways by various upstream factors in different cell types are myriad.

Though a comprehensive summary of the roles of MAPK pathways in tissue fibrosis falls well outside the scope of this

article, it is worth mentioning here some examples of the implications of MAPK pathway signaling for study of fibrosis. Numerous preclinical animal studies have demonstrated that development of tissue fibrosis in several organs is associated with activation of p38 which, when inhibited, blunts the development of fibrotic pathology[13, 14, 15, 16, 17, 18, 19]. Specifically, pathological activation of p38 drives myofibroblast precursors to differentiate into myofibroblasts. Inhibition of p38 has been demonstrated to antagonize fibroblast differentiation and pro-fibrotic gene expression *in vitro* as well[20, 21, 22, 23]. The resultant antagonism of myofibroblast formation and subsequent tissue fibrosis upon p38 inhibition are at least in part a consequence of non-canonical activation of p38 signaling by TGF-β. Under the non-canonical paradigm, TGF-β can activate p38 signaling *via* TAK1 and MKK3/6, leading to cross-talk with other cytokines that modulate upstream activity of the same pathways. TGF-β-induced p38 signaling can also provide feedback to modulate canonical TGF-β/SMAD signaling through phosphorylation of the linker region of SMAD proteins, affecting subcellular location of these proteins with consequent effects on expression of extracellular matrix-associated genes, which is a paradigm likely relevant to the role of p38 signaling in fibrosis[24]. In this way, TGF-β can drive activity that can blunt or enhance the signaling of other pathways, including modulatory effects on its own signaling *via* feedback loops. Other roles for MAPK signaling in fibroblasts include modulating cellular proliferation and expression of extracellular matrix-associated, pro-fibrotic genes[20,21,25, 26, 27], demonstrating broad relevance for these pathways in fibroblast biology during wound healing.

1.1.2.3. PI3K/Akt signaling

Another molecular pathway clearly implicated in fibrotic pathophysiology is PI3K/Akt signaling. Often induced as a result of receptor tyrosine kinase signaling, PI3K/Akt activation can also be induced by TGF-β signaling and drive TGF-β-induced effects[28, 29, 30]. Heightened activation of PI3K/Akt has been reported in animal models of fibrosis in multiple tissues including lung[31,32], liver[33, 34, 35], skeletal muscle[36], and in dermal fibroblasts from human patients with systemic sclerosis[37, 38, 39]. PI3K/Akt signaling is often understood to control cell survival and resistance to apoptosis. Thus, it is not surprising that numerous reports demonstrate either direct anti-fibrotic activity of PI3K/Akt inhibitors on animal models of fibrosis, or dependence of anti-fibrotic agents *in vitro* or *in vivo* on inhibition of PI3K/Akt signaling, including demonstration of PI3K/Akt-dependent suppression of differentiation of myofibroblast precursors or induction of myofibroblast apoptosis[33,37,40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53]. Thus, another mechanism through which anti-fibrotic compounds may be able to act is *via* suppression of PI3K/Akt signaling, particularly in myofibroblasts or myofibroblast precursors, inhibiting differentiation and/or survival.

1.1.3. Challenges associated with the treatment of organ fibrosis

Though understanding the basic science of fibrosis has progressed substantially over the past several decades, development of clinically successful therapeutics has lagged greatly behind elucidation of key mechanisms underlying the development, progression, and maintenance of tissue fibrosis. Although nintendanib and pirfenidone were recently approved and recommended conditionally for treatment of idiopathic pulmonary fibrosis with moderate confidence in effect estimates[54], the results of development and clinical testing of anti-fibrotic pharmaceutical products for other fibrotic diseases have been, at best, disappointing. Walraven and Hinz[55] cogently explain major factors underlying the difficulties in developing successful anti-fibrotic therapeutics. These complicating factors include positive feedback loops between the pathophysiological tissue stiffness characteristic of fibrosis and the cells effecting the fibrotic response, redundancy in the upstream molecular pathways that promote development and maintenance of tissue fibrosis, and the stealth with which many fibrotic disease states progress prior to the development of clinical symptoms that arise only during late-stage disease. Thus, purportedly anti-fibrotic pharmaceutical therapies that seek to block only one molecular pathway are likely to fail, favoring the development of broader spectrum agents that target through multiple molecular pathways and/or those that target myofibroblasts directly. Thus, we review in this article recent evidence in the published literature that implicates artemisinin and its derivatives as potential therapeutics for multiple fibrotic diseases through their pleiotropic therapeutic effects.

1.2. Artemisinin

1.2.1. Artemisinin and its derivatives

Artemisinin is an endoperoxide bridge-containing sesquiterpene lactone that was discovered in China by Project 523 in conjunction with Dr. Tu Youyou in 1972 as an extracted chemical product produced by the plant *Artemisia annua*[56,57]. The notoriously poor solubility of artemisinin in water and oil has led to the synthesis of several chemical derivatives aimed at increasing its solubility without sacrificing the structural factors responsible for its therapeutic efficacy (Fig. 2). Thus, these chemical derivatives can be delivered using standard pharmacologic solvents and constitute the majority of artemisinin-like compounds used in preclinical animal models and in clinical patients. Artemisinin was originally used millennia ago by the ancient Chinese people for its ability to treat "fever" often thought to be malaria[58], and indeed this compound and its derivatives remain critical for treatment of malaria to this day. More recent investigation has also demonstrated efficacy of these compounds for treatment of numerous other disease states including inflammation, infection, cancer, and fibrosis59, 60, 61, 62, 63.

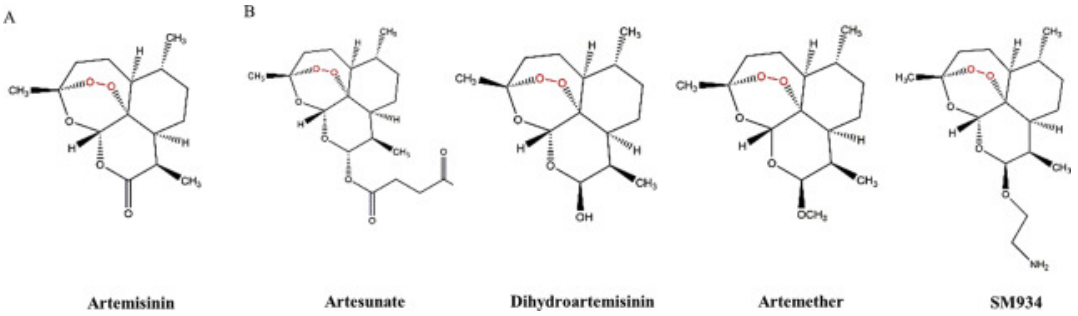

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Figure 2. Structures of artemisinin and its derivatives. (A) Artemisinin is a sesquiterpene lactone compound derived from the plant *Artemisia annua*. (B) Chemical derivatives of artemisinin including artesunate, dihydroartemisinin, artemether, and SM934 have been synthesized to increase solubility of the drug in specific types of solvents. The pharmacologic efficacy of these compounds depends on an endoperoxide bridge, in the form of a 1,2,4-trioxane ring, in each of these molecules (highlighted in red).

1.2.2. Mechanisms of action

The implication of artemisinin-based drugs in such varied disease states suggests broad, pleiotropic effects underlying their pharmacology; though their mechanisms of action are not entirely understood, the available data suggest that this is the case. Generally, the mechanism of action of artemisinin is understood to require the endoperoxide bridge. The reaction of the endoperoxide bridge with ferrous iron, such as that found in heme, results in generation of reactive oxygen species (ROS), which can result in a myriad of downstream cytostatic and cytotoxic effects which, in part, likely serves to explain the pleiotropic effects of artemisinin, since the effects of reactive oxygen species on a cell are also myriad[64]. In high quantities, reactive oxygen species can cause cellular damage through formation of lesions and mutations in genomic and mitochondrial DNA, peroxidation of membrane lipids, and activation of pro-apoptotic pathways, among other effects[65].

While the ability of artemisinin compounds to form ROS and lead to cellular damage is doubtlessly critical to their broad pharmacologic properties, recent evidence has suggested other complementary mechanisms of action. A recent report demonstrated that artesunate potently inhibits EXP1, a previously uncharacterized glutathione-*S*-transferase expressed in the membrane of the malaria parasite *Plasmodium falciparum* responsible for degradation of hematin[66].

Another recent report described 124 proteins in *P. falciparum* as direct artemisinin binding targets, many of which are involved in critical metabolic processes in the parasite. In addition, artemisinin covalently bound numerous proteins in a human colon cancer cell line, and the extent to which proteins in this line were bound by artemisinin directly was shown to correlate with the cytotoxicity of artemisinin in these cells, suggesting that covalent binding of target proteins is at least partially responsible for artemisinin's cytotoxic activity[67]. Most recently, Gotsbacher et al.[68] used a reverse proteomic screen, identifying and validating the protein "BCL-2-associated agonist of cell death" (BAD) as a target of artesunate. Treatment of HeLa cells with artesunate resulted in concentration-dependent inhibition of BAD phosphorylation at serine 136 and subsequent concentration-dependent decrease in BCL-XL protein expression. Artesunate also demonstrated synergy with the topoisomerase inhibitor camptothecin, suggesting potential clinical utility in this context[68]. These reports, demonstrating direct eukaryotic (and, more specifically, mammalian) protein targets of artemisinin compounds may help explain the anti-fibrotic therapeutic effects of these compounds summarized in this review.

2. Artemisinin and its derivatives alleviate development or progression of tissue fibrosis in experimental animal models

The effects of artemisinin and its derivatives as antagonists of the development or progression of fibrotic phenotypes have been characterized in fibrotic models across multiple tissues, suggesting potential utility of these compounds for treatment of several fibrotic disease states.

2.1. Artemisinin compound effects in pulmonary fibrosis

In a rat model of pulmonary fibrosis induced by intratracheal bleomycin, daily intraperitoneal (i.p.) injections of artesunate suppressed expression of α-SMA and type IV collagen in the lungs. I.p. administration of artesunate also suppressed bleomycin-induced expression of notch signaling-related proteins including NOTCH1, JAGGED1, HES1, and the Notch intracellular domain (NICD). In primary rat lung fibroblasts, artesunate also antagonized TGF-β1-mediated expression of α-SMA, as well as expression of notch family members NOTCH1, JAGGED1, HES1, and NICD. These data suggest that artesunate-mediated suppression of experimental pulmonary fibrosis proceeds at least in part by suppression of notch signaling in lung fibroblasts, leading to decreased fibroblast activation and a resultant dampening of the fibrotic response induced by pulmonary insult[69]. In another report of bleomycin-induced pulmonary fibrosis, daily i.p. administration of artesunate blunted the development of pulmonary fibrosis and lung damage in rat as assessed by histological analysis. Artesunate inhibited bleomycin-induced increase in type IV collagen protein in whole lung tissue and type IV collagen transcript expression in lung fibroblasts. Artesunate treatment also led to increased expression of matrix metalloproteinase (MMP)-2 and MMP-9 protein in whole lung tissue and transcript expression in lung fibroblasts. Artesunate also blunted the bleomycin-induced upregulation of tissue inhibitor of metalloproteinase (TIMP)-1 and TIMP-2 in whole lung tissue and transcript expression in fibroblasts[70]. These data suggest that artesunate blunts the fibrotic pulmonary response at least in part through modulating the MMP to TIMP ratio in lung fibroblasts, promoting degradation of excess extracellular matrix (ECM).

In a rat model of bleomycin-induced pulmonary fibrosis, daily i.p. administration of dihydroartemisinin (DHA) blunted the fibrotic response, subsequently decreasing collagen content in the lung. DHA administration dose-dependently attenuated bleomycin-induced upregulation of TGF-β1, TNF-α, α-SMA, and p65 in the lungs as measured by immunohistochemical analysis, qRT-PCR, and Western blot. These data suggested that DHA attenuates pulmonary fibrosis at least in part through suppression of canonical inflammatory and pro-fibrotic pathways including TNF-α, TGF-β1, and NF-κB[71]. In further studies using a bleomycin-induced model of pulmonary fibrosis in rat, daily i.p. injection of artesunate decreased bleomycin-induced mortality and reduced fibrotic pathology as assessed by lung histology. Artesunate treatment blunted bleomycin-induced expression of HSP47-encoding and Col I-encoding transcripts, as well as α-SMA, HSP47, SMAD3, and TGF-β1 protein in the lung, suggesting that artesunate-mediated

suppression of bleomycin-induced pulmonary fibrosis is mediated by antagonism of TGF-β signaling, as well as by inhibiting expression of genes governing collagen synthesis and maturation[72]. Intragastric administration of DHA also attenuated the fibrotic response in a mouse model of paraquat-induced pulmonary fibrosis, as indicated by reduced TGF-β1 expression in lung and comparatively mild inflammation and edema in relation to mice that were not treated with DHA[73]. In a rat intratracheal bleomycin model of pulmonary fibrosis, i.p. artesunate resulted in reduced development of pulmonary fibrosis as assessed by histological analysis, resulting in lower levels of TGF-β1 and TNF-α in rat serum[74]. In another report, artesunate treatment decreased pulmonary inflammation and lung fibrosis resulting from bleomycin-induced pulmonary fibrosis in rats. Artesunate also reduced the amount of TGF-β1 in the bronchoalveolar lavage fluid and the collagen content in the lung[75]. Taken together, these reports suggest that artemisinin compounds antagonize experimental pulmonary fibrosis at least in part through their effects on lung fibroblasts and are effected through inhibition of canonical pro-fibrotic TGF-β signaling, inhibition of pro-inflammatory NF-κB signaling, inhibition of notch signaling, and regulation of ECM homeostasis through modulation of the expression of genes encoding ECM proteins, as well as through regulation of proteinase activity *via* modulation of MMP and TIMP levels.

2.2. Artemisinin compound effects in renal fibrosis

In a rat unilateral ureteral obstruction (UUO) model of kidney fibrosis, treatment with artesunate resulted in decreased renal expression of connective tissue growth factor (CTGF) and α-SMA, suggesting suppression of fibrotic phenotypes[76]. In a rat model of subtotal nephrectomy, oral artemisinin resulted in attenuation of nephrectomy-induced renal damage, as measured by changes in *N*-acetyl-β-D-glucosaminidase (NAG) activity, blood urea nitrogen (BUN), and serum creatinine (sCr), as well as by histological assessment, demonstrating that pharmacologic artesunate suppressed the loss of functional filtration associated with kidney fibrosis and loss of kidney function. Artemisinin treatment also resulted in reduced macrophage accumulation and antagonized nephrectomy-induced increases in α-SMA, CTGF, and FSP1 expression, indicating a reduction in the degree of renal inflammation and fibrosis after artemisinin treatment. Artemisinin treatment lessened upregulation of NLRP3 and ASC in tubular epithelial cells *in vivo*, suggesting activation of the NLRP3 inflammasome as a consequence of nephrectomy, which is then blunted by treatment with artemisinin. Accordingly, nephrectomy-induced upregulation of NLRP3, caspase 1, IL-18, and IL-1β was antagonized by artemisinin treatment. In immortalized human kidney tubular epithelial cells cultured *in vitro*, artemisinin antagonized angiotensin II-mediated induction of NLRP3, caspase 1, IL-18, and IL-1β and prevented colocalization of NLRP3 and ASC, as assessed by immunofluorescent analysis. Artemisinin treatment rescued nephrectomy-induced reduction of IκBα and attenuated nephrectomy-induced nuclear accumulation of p65. In human kidney tubular epithelial cells, artemisinin rescued Ang II-mediated downregulation of IκBα and antagonized Ang II-mediated p65 nuclear accumulation. Taken together, the data from this report suggest that artemisinin inhibits nephrectomy-induced NF-κB activation and inflammasome activity in the kidney, resulting in suppression of inflammation and fibrosis[77].

In a rat UUO model of kidney fibrosis, daily administration of artesunate antagonized UUO-mediated renal dysfunction as measured by serum BUN, sCr, and change in kidney mass to body mass ratio. Artesunate administration also reduced renal fibrosis, assessed by Masson's trichrome staining, and inflammation, assessed by staining of renal macrophages. Artesunate antagonized UUO-mediated increases in expression of fibronectin, Col I, and α-SMA, and rescued UUO-mediated loss in expression of E-cadherin. Artesunate partially rescued UUO-mediated decrease in bone morphogenetic BMP7 levels in the kidney, and artesunate also antagonized UUO-mediated increase in USAG-1 expression. Data from this report suggest that artesunate attenuates the kidney fibrotic response by suppressing pro-fibrotic gene expression, possibly by inhibiting the epithelial-to-mesenchymal transition in kidney epithelial cells, thus resulting in decreased accumulation of myofibroblasts. Additionally, this report suggests that artesunate inhibits the inflammatory response in the kidney and rescues the USAG-1/BMP-7 ratio that is elevated by the fibrotic kidney insult[78]. In a rat model of passive heymann nephritis (PHN), oral administration of the artemisinin analogue SM934 (structure shown in Fig. 2) attenuated PHN-mediated kidney dysfunction as measured by aberrant proteinuria, serum

albumin, and circulating IgG antibodies. The change in ratio of kidney weight to body weight induced by PHN was rescued by SM934 administration, as was the induction of tubular protein cast, tubular damage, and tubulointestinal inflammatory cell infiltration. SM934 treatment diminished rat glomerular IgG deposition that was induced by PHN and protected against podocyte injury to maintain integrity of the glomerular filtration barrier. SM934 substantially attenuated PHN-mediated collagen deposition in the kidney, as well as α-SMA and CD68 protein expression, suggesting the presence of fewer myofibroblasts and macrophages in the kidney respectively. SM934 also significantly reduced PHN-induced upregulation of TGF-β1 and activation of SMAD2 and SMAD3, while rescuing PHN-mediated suppression of SMAD7 expression, thus driving a gene expression paradigm suggestive of inhibited TGF-β activity. In normal human proximal tubular epithelial cells, SM934 antagonized C3a-mediated EMT as determined by suppression of type I collagen transcript expression, α-SMA protein expression, and through rescue of C3a-suppressed E-cadherin expression. Taken together, data from this report suggest that the artemisinin analogue SM934 imparts renal protective effects against a rodent model of membranous nephropathy, suppresses the fibrotic response at least in part through antagonizing canonical TGF-β signaling, maintaining the glomerular filtration barrier through podocyte protection, and potentially inhibiting EMT in renal epithelial cells, thus suppressing fibrotic phenotypes and protecting against loss of renal function[79].

In another report describing a set of experiments performed in a streptozotocin (STZ)-induced rat model of diabetic nephropathy, administration of artemisinin *via* oral gavage resulted in reduced kidney damage and dampened loss of kidney function. Transcriptomic analysis of kidney tissue from these rats demonstrated that the differential expression of a subset of genes induced by STZ treatment was attenuated by co-administration of artemisinin, suggesting that artemisinin antagonized some of the molecular effects driving diabetic nephropathy in this model. Among the genes whose differential expression by STZ was blunted by administration of artemisinin were several genes causally involved in fibrotic pathology[80]. In a report of a UUO-induced murine model of kidney fibrosis, daily intragastric administration of DHA resulted in partial preservation of kidney function and limitation of renal hypertrophy. DHA administration attenuated UUO-mediated upregulation of fibronectin and types I and III collagen, antagonized fibroblast differentiation as assessed by expression of α-SMA, and limited the number of proliferative fibroblasts in the kidney as measured by the number of cells co-staining for FSP1 and PCNA in renal tissue. Analysis of signal transduction pathways revealed that DHA antagonized UUO-mediated activation of PI3K/Akt signaling, suggesting that inhibition of activation of these pathways is responsible at least in part for the anti-fibrotic effects of DHA in renal fibrosis[81]. Together, these reports suggest that artemisinin derivatives antagonize development of renal fibrosis and loss of renal function in multiple animal models resulting from various insults *via* reduction of inflammation and inflammasome activation, antagonism of TGF-β signaling, and suppression of myofibroblast-forming EMT in renal epithelial cells.

2.3. Artemisinin compound effects in hepatic fibrosis

I.p. administration of DHA dose-dependently decreased hydroxyproline content in liver and blood in a rat bile duct ligation (BDL) model of liver fibrosis. This response was concomitant with decreases in serum markers of liver fibrosis, decreases in liver α-SMA and PDGF-B, and rescued expression of peroxisome proliferator-activated receptor PPARγ. DHA failed to induce cytotoxic effects at concentrations from 1 to 40 μmol/L in human hepatocytes *in vitro*, while treatment with 5–30 μmol/L DHA reduced viability significantly in both human and rat hepatic stellate cells (HSCs) *in vitro*. Treatment with 5–20 μmol/L DHA-induced antiproliferative effects in HSCs and induced cell cycle arrest *via* upregulation of p53 and p21, as well as *via* downregulation of CDK2 and cyclin A. DHA treatment reduced expression of pro-fibrotic HSC activation markers, including α-SMA, Col I, and fibronectin, as well as of PDGF-RB, TGF-βRI, TGF-βRII, and EGFR, while increasing expression of PPARγ. DHA also concentration-dependently reduced ERK phosphorylation, and co-treatment with DHA and PDGF-RB inhibitor imatinib reduced expression of pro-fibrotic markers Col I, fibronectin, and α-SMA beyond the reduction observed upon treatment with imatinib alone, suggesting cooperative effects of these drugs. Taken together, data from this report suggest that DHA dose-dependently inhibits development

of liver fibrosis through its growth inhibitory effects *via* p53/p21 on potentially fibrogenic hepatic stellate cells, and through antagonism of PDGF-RB/ERK-mediated HSC activation and the subsequent increase in expression of pro-fibrotic genes[82].

In a rat BDL model of liver fibrosis, i.p. injection of DHA resulted in diminished BDL-induced liver dysfunction as measured by attenuated increase in levels of serum alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), and bilirubin, as well as attenuated increase in liver/body mass ratio. DHA also antagonized BDL-induced expression of pro-inflammatory cytokines TNF-α and IL-6 in the liver as well as in the blood. DHA administration also dampened BDL-induced hepatic fibrogenesis as measured by suppression of BDL-induced α-SMA, type I collagen, fibronectin, TGF-βRII, PDGF-RB, and EGFR protein expression. DHA treatment increased cleaved caspase 3 in the liver and decreased the BCL-2/BAX ratio, suggesting that DHA treatment promoted sensitivity to apoptosis in profibrogenic hepatic stellate cells. Accordingly, in primary rat hepatic stellate cells, *in vitro* treatment with DHA concentration-dependently reduced viability and resulted in substantial apoptosis, whereas DHA promoted only minimal apoptosis at the same concentrations in a human fetal hepatocyte line, demonstrating that the apoptotic effects of DHA in the liver at pharmacologically relevant concentrations are likely limited to hepatic stellate cells and result in minimal damage to hepatocytes. DHA-induced hepatic stellate cell apoptosis proceeded *via* the mitochondrial pathway (caspase 9/3) and acted *via* DHA-mediated disruption of PI3K/Akt signaling; treatment with a typical PI3K chemical inhibitor phenocopied the effects of DHA on HSC apoptosis, suggesting a mechanism of action for this phenomenon, consistent with the well-established role of PI3K/Akt signaling in promotion of cell survival. Treatment of hepatic stellate cells with DHA also antagonized PDGF-induced expression of PDGF-RB, TGF-βRII, and EGFR. Together, data from this report suggest that DHA suppresses fibrogenesis induced by BDL, leading to dampened inflammation and damage in the liver. This suppression of fibrogenesis likely proceeds at least in part through inhibition of PI3K/Akt, leading to mitochondrial pathway apoptosis in fibrogenic hepatic stellate cells *in vivo*, as well as through downregulation of pro-fibrotic gene expression including PDGF-RB and TGF-βRII, leading to dampening of downstream fibrotic responses in hepatic stellate cell-derived myofibroblasts[83]. Another recent report demonstrated that DHA antagonized carbon tetrachloride (CCl_4)-induced hepatic fibrosis in rat through induction of senescence in hepatic stellate cells through an autophagic, GATA6/JNK-dependent mechanism, preventing stellate cell activation and subsequent fibrosis[84]. This suggests that another mechanism by which DHA administration blunts hepatic fibrosis proceeds *via* inducing senescence in otherwise potentially fibrogenic hepatic stellate cells, preventing them from differentiating into myofibroblasts and depositing fibrotic collagen.

In a hepatic fibrosis CCl_4 rat model, oral artesunate decreased expression of TNF-α and IL-6 in liver tissue and relieved liver damage, inflammatory cell infiltrate, and steatosis. Oral artesunate also substantially reduced induction of collagen and α-SMA expression in this liver fibrosis model and antagonized nuclear localization of NF-κB p65 in the liver, indicating that artesunate blunted NF-κB signaling activity. After induction of hepatic fibrosis by CCl_4, oral artesunate reduced expression of TGF-β, α-SMA, TLR4, MyD88, and p65, suggesting that the anti-fibrotic mechanism of artesunate in the liver was based at least in part on TLR4/MyD88/NF-κB signaling. There was also no notable artesunate liver toxicity at the therapeutic doses used in this study. Overall, these data suggest that artesunate inhibits formation of liver fibrosis by acting protectively and blunting the TLR4/MyD88/NF-κB pathway, likely in hepatic stellate cells, preventing activation of the formative cells of liver fibrosis in this model[85].

In a rat model of bovine serum albumin (BSA)-induced hepatic fibrosis, intragastric administration of artesunate resulted in attenuation of induced histopathological liver damage. Artesunate treatment also reduced the amount of collagen deposition induced by BSA injection, as assessed by liver histology and quantification of hepatic hydroxyproline content. Artesunate decreased BSA-mediated increases in α-SMA and type I collagen expression in the liver, while increasing expression of MMP-2, MMP-9, and MMP-13. These data suggest that the antagonistic effects of artesunate on development of hepatic fibrosis may be due at least in part to suppression of hepatic stellate cell activation and increased collagenase activity *via* regulatory of protease activity by modifying the MMP/TIMP ratio[86]. In

a mouse model of *Schistosoma japonicum* infection, administration of artesunate antagonized infection-mediated liver dysfunction as measured by serum levels of ALT, AST, and hyaluronic acid (HA). Artesunate also antagonized infection-mediated liver fibrosis as assessed by liver hydroxyproline content, as well as by expression of genes encoding TGF-β1, α-SMA, and VEGF, as well as by type I collagen, type III collagen, and VEGF protein expression. This suggests that artesunate has the potential to limit the extent of liver fibrosis caused by another, pathophysiologically distinct type of liver insult[87].

In a mouse model of CCl_4-induced liver fibrosis, daily i.p. injections of artemether blunted CCl_4-induced development of histological signs of liver fibrosis, as well as hydroxyproline content, AST, ALP, and ALT levels in the serum and in the liver. Artemether treatment resulted in reduced liver expression of α-SMA, fibronectin, and type I collagen induced by administration of CCl_4, as well as reduced expression of EGFR and PDGF-RB, suggesting that artemether attenuates hepatic stellate cell activation *in vivo*. Accordingly, rat hepatic stellate cells cultured *in vitro* and treated with artemether demonstrated a concentration-dependent reduction in expression of α-SMA, fibronectin, type I collagen, TGF-βRI, PDGF-RB, and EGFR transcript and protein, further supporting this idea. Hepatic stellate cells demonstrated a concentration-dependent antiproliferative response to artemether *in vitro*, while the same concentrations of artemether failed to induce cytotoxicity in hepatocytes as assessed by lactate dehydrogenase (LDH) activity. Hepatic stellate cells treated with artemether demonstrated aberrant mitochondrial morphology and gene expression, and metabolic profiles reminiscent of ferroptosis, including increased levels of iron and lipid peroxidation products, decreased GSH and NADPH levels, increased expression of ROS1, and decreased expression of GPX4 and SLC7A11. A ferroptosis-specific inhibitor, Fer-1, partially attenuated artemether-mediated effects on ferroptosis-associated gene expression. Fer-1 also attenuated artemether-mediated effects on expression of α-SMA, type I collagen, fibronectin, TGF-βRI, EGFR, and desmin. Artemether treatment induced expression and nuclear localization of p53 in hepatic stellate cells, and siRNA-mediated knockdown of p53 blunted the effects of artemether on expression of ferroptotic proteins SLC7A11, GPX4, and ROS1, as well as its effects on expression of α-SMA, fibronectin, type I collagen, PDGF-RB, and TNF-α. Together these data suggest that the therapeutic effects of artemether treatment on development of experimental hepatic fibrosis occur at least in part due to inhibition of hepatic stellate cell activation as well as p53-mediated ferroptotic effects[88].

In a rat model of BSA-induced liver fibrosis, oral administration of artesunate resulted in blunting of the fibrotic response as assessed by hepatic collagen deposition and by expression of α-SMA and TGF-β1. The same report described that, in a rat hepatic stellate cell line, artesunate concentration-dependently inhibited transcription of the gene encoding type I collagen, providing further evidence that the anti-fibrotic effects of artesunate in the liver are likely due at least in part to its effects on hepatic stellate cells[89]. In a BSA-induced rat model of hepatic fibrosis, artesunate antagonized the pathological increase in expression of MMP-2, MMP-9, and type I collagen, and artesunate induced expression of MMP-13[90], suggesting that the anti-fibrotic effects of artesunate on hepatic fibrosis may be due at least in part to its effects on expression of ECM-associated proteases as well. Taken together, these reports demonstrate that artemisinin derivatives potently inhibit hepatic fibrosis in several experimental models largely through their apoptotic and anti-fibrotic effects on pro-fibrogenic hepatic stellate cells, as well as through regulation of collagenase activity, thus limiting the extent of development and maintenance of hepatic fibrosis.

2.4. Effects of artemisinins in other types of tissue fibrosis

In a rat myocardial infarction (MI) model induced by ligation of the left anterior descending coronary artery, rats administered artemisinin by oral gavage showed a significant increase in survival out to 30 days post-operative. Left ventricular function improved along with cardiac function in the group of rats administered artemisinin, as determined by hemodynamics and echocardiographic measurements, and therapeutic artemisinin attenuated cardiomyocyte hypertrophy caused by the cardiac insult. Histological analysis demonstrated that artemisinin also blunted the fibrotic response to MI in both the perivascular space and the interstitial space of the non-infarct area. Artemisinin-treated

infarcted rats demonstrated a lower p-IκBα/IκBα ratio, indicating less activation of NF-κB signaling in response to artemisinin. Artemisinin also blunted the MI-induced increase in protein levels of type I collagen, TGF-β1, MMP-2, and MMP-9. Taken together, these data suggest that artemisinin attenuates myocardial infarct-induced cardiac hypertrophy and cardiac fibrosis at least in part *via* suppression of NF-κB and TGF-β signaling and inhibits pathophysiological cardiac remodeling at least in part by suppressing MI-induced collagenase expression[91]. In a high fat diet-induced murine model of atherosclerosis, daily oral administration of artemisinin protected against development of atherosclerotic lesions as assessed by reduced smooth muscle cell hyperplasia and blunted fibrosis in the aortic intima. Artemisinin administration suppressed activation of NF-κB signaling and the NLRP3 inflammasome in the aorta, likely due to activation of AMP-activated protein kinase (AMPK) signaling in aortic macrophages[92].

In rat epidural fibrosis scar tissue fibroblasts, artesunate inhibited fibroblast proliferation in a concentration-dependent manner, as evidenced by reduced cellular proliferation, an increased population fraction of 4n cells by flow cytometry indicating a G2/M phase arrest, and decreased protein levels of PCNA and cyclin D1. Artesunate treatment of fibroblasts yielded formation of autophagosomal vacuoles as shown by transmission electron microscopy and Western blot analysis of proteins associated with autophagic flux. Inhibition of the autophagy cascade with an autophagy inhibitor attenuated artesunate-mediated inhibition of cell growth *via* antagonism of the artesunate-mediated increase in p53 and p21 proteins. In an *in vivo* rat model of epidural fibrosis, treatment with artesunate reduced the degree of epidural fibrosis according to Rydell's classification. Artesunate-treated rats demonstrated a dose-dependent reduction in the number of fibroblasts at the laminectomy operation site, a dose-dependent reduction in collagen, and a dose-dependent reduction in the fraction of $PCNA^+$ cells. Taken together, these data suggest that artesunate likely inhibits epidural fibrosis *in vivo via* autophagy-mediated induction of p53/p21 signaling in fibroblasts, leading to cell cycle arrest and thus preventing fibroblast proliferation and fibrosis[93].

In a rabbit model of knee arthrofibrosis, intragastric administration of artesunate significantly decreased the number of fibroblasts and degree of fibrosis in the intraarticular tissue through autophagy driven by inhibition of mechanistic target of rapamycin (mTOR) signaling[94]. In a rat model of compression-induced sciatic nerve injury, application of artesunate to the injury region through a resorbable gelatin sponge resulted in enhanced peripheral nerve regeneration as assessed by improved sciatic nerve function, reduced fibroblast presence and fibrosis, dampened inflammation, and increased myelinated axon diameter, suggesting that artesunate-enhanced nerve regeneration proceeds alongside suppression of inflammatory and fibrotic responses[95]. In a rabbit ear model of hypertrophic scarring, application of cream containing either artemisinin or artesunate led to improved scar appearance, lessened hypertrophy, reduced volume of fibroblasts, and a greater degree of alignment of collagen fibers[96]. In another report using a rabbit ear hypertrophic scar model, topical application of artesunate in a cream formulation resulted in a significant decrease in scar hypertrophy and decreased expression of dermal TGF-β1 and SMAD3 protein, suggesting that artesunate alleviates the formation of hypertrophic scar in the skin *via* downregulation of profibrotic TGF-β family signal transducers[97]. In a rabbit model of intraarticular scar adhesion induced by surgical removal of cortical bone, local injection of artesunate dose-dependently reduced the number of fibroblasts and the deposition of collagen in the scar tissue, suggesting that artesunate may be an effective therapeutic for suppression of intraarticular fibrotic adhesion[98]. Taken together, these data suggest that artemisinin derivatives are effective as pharmacologic agents to prevent the development and progression of tissue fibrosis in organs other than the lung, liver, and kidney, through broad inhibition of inflammatory and pro-fibrotic signaling.

The *in vivo* anti-fibrotic literature described above regarding artemisinin compounds is summarized in Table 1[69], [70], [71], [72], [73], [74], [75], [76], [77], [78], [79], [80], [81], [82], [83], [84], [85], [86], [87], [88], [89], [90], [91], [92], [93], [94], [95], [96], [97], [98].

Table 1. Summary of preclinical antifibrotic reports of artemisinin compounds.

Modeled disease	Animal model	Drug	Ref.

Pulmonary fibrosis	Rat intratracheal bleomycin	Artesunate	69
		Artesunate	70
		Dihydroartemisinin	71
		Artesunate	72
	Mouse intragastric paraquat	Dihydroartemisinin	73
	Rat intratracheal bleomycin	Artesunate	74
		Artesunate	75
Renal fibrosis	Rat unilateral ureteral obstruction	Artesunate	76
	Rat subtotal nephrectomy	Artemisinin	77
	Rat unilateral ureteral obstruction	Artesunate	78
	Rat passive heymann nephritis	SM934	79
	Rat STZ-induced diabetic nephropathy	Artemisinin	80
	Mouse unilateral ureteral obstruction	Dihydroartemisinin	81
Hepatic fibrosis	Rat bile duct ligation	Dihydroartemisinin	82
		Dihydroartemisinin	83
	Rat intraperitoneal CCl_4	Dihydroartemisinin	84
	Rat subcutaneous CCl_4	Artesunate	85
	Rat intravenous BSA	Artesunate	86
	Mouse *S. japonicum* injection	Artesunate	87
	Mouse intraperitoneal CCl_4	Artemether	88
	Rat intravenous BSA	Artesunate	89
		Artesunate	90
Cardiac fibrosis	Rat coronary artery ligation	Artemisinin	91
Atherosclerosis	Mouse high fat diet	Artemisinin	92
Epidural fibrosis	Rat laminectomy	Artesunate	93
Arthrofibrosis	Rabbit cortical bone removal	Artesunate	94
Sciatic nerve injury	Rat sciatic nerve compression	Artesunate	95
Dermal fibrosis	Rabbit ear hypertrophic scar	Artemisinin/Artesunate	96
		Artesunate	97
Intraarticular scar adhesion	Rabbit cortical bone removal	Artesunate	98

3. Cellular effects of artemisinin derivatives on cells and cellular pathways causally associated with fibrosis

The *in vivo* reports summarized above present a strong case that artemisinin derivatives may be effective against

multiple types of tissue fibrosis. Reports of the effects of artemisinin and its derivatives *in vitro* on cells associated with fibrotic pathogenesis lend further insight into the mechanisms behind the anti-fibrotic effects of these compounds.

3.1. Anti-proliferative and pro-apoptotic effects

Several reports have described anti-proliferative and pro-apoptotic effects of artemisinin derivatives, including effects on myofibroblast precursors *in vitro*. In human embryonic lung fibroblasts, treatment with artesunate inhibited proliferation and induced apoptosis, concordant with a concentration-dependent increase in the expression of genes encoding FAS, FASL, and caspase 3[99]. In primary human fibroblasts, artesunate induced apoptosis through concentration dependent induction of endoplasmic reticulum stress that was dependent on activation of PERK[98]. In another report, artesunate concentration-dependently inhibited proliferation of human embryonic lung fibroblasts through induction of a G0/G1 arrest, and induced apoptosis through upregulation of caspase 3[100]. In human fibroblast-like synoviocytes (FLS) cultured *in vitro*, artesunate inhibited cellular proliferation and induced cellular apoptosis in a concentration-dependent manner[101]. In primary human airway smooth muscle cell cultures, artesunate treatment led to downregulation of cyclin D1, inhibition of cellular proliferation, and attenuated activation of Akt by fetal bovine serum. The anti-proliferative effects of artesunate on smooth muscle cells were also demonstrated *in vivo* in a murine model of ovalbumin-induced allergic asthma[102]. In a rat hepatic stellate cell line, increasing artesunate concentration inhibited cellular proliferation as demonstrated by induction of a G0/G1 arrest[103], and inhibition of proliferation in rat hepatic stellate cells was also described in other reports[104,105]. In a human hepatic stellate cell line, artesunate concentration-dependently reduced cellular viability *via* induction of apoptosis[106]. Artesunate also induced apoptosis in rat glomerular mesangial cells in a concentration-dependent manner through downregulation of BCL-2 protein[107], which may be responsible at least in part for the antagonistic effects of artemisinin compounds towards renal fibrosis *in vivo*, as mesangial cells likely contribute to renal fibrosis through differentiation into myofibroblasts, at least in certain contexts[108]. Treatment of human kidney fibroblasts with DHA also led to antagonism of TGF-β-induced proliferation[81]. Taken together, these reports suggest that the anti-fibrotic effects of artemisinin drugs may act at least in part through broad suppression of proliferation and/or induction of apoptosis in potentially fibrogenic myofibroblast precursors.

3.2. Suppression of myofibroblast differentiation and pro-fibrotic gene expression

Besides their anti-proliferative and pro-apoptotic effects, artemisinin compounds also inhibit myofibroblast differentiation and downregulate pro-fibrotic gene expression in numerous cell types.

Artesunate treatment antagonized expression of pro-fibrotic genes in human skin fibroblasts cultured *in vitro*, resulting in a gene expression paradigm characterized by increased expression of MMPs and decreased expression of myofibroblast markers, while also inducing fibroblast apoptosis[109]. Treatment of human embryonic lung fibroblasts with artesunate resulted in concentration-dependent decreases in collagen deposition as well as expression of the genes encoding type I and III collagen, suggesting that artesunate-induced reduction of fibroblast collagen production is due at least in part to downregulation of collagen-encoding transcripts[110]. A recent report detailing protective effects of artesunate against arthrofibrosis in a rabbit knee model also characterized the effects of artesunate on human fibroblasts. Treatment of fibroblasts with artesunate resulted in concentration-dependent and time-dependent decreases in fibroblast proliferation and inhibition of mTOR signaling *via* activation of AMPK and inhibition of PI3K. Inhibition of mTOR led to subsequent increase in expression of beclin-1 and construction of the autophagosome, and knockdown of beclin-1 desensitized fibroblasts to the growth arrest and pro-apoptotic effects induced by artesunate. This report suggests a mechanism by which artesunate application might attenuate development of fibrosis in the surgery-induced arthrofibrosis model *via* inhibitory effects on fibroblast proliferation and promotion of autophagosomal activity[94].

In FLS isolated from patients with rheumatoid arthritis, artesunate treatment concentration-dependently inhibited

cellular migration and invasion, led to a decrease in p-Akt, and resulted in downregulation of MMP-9 protein. Due to the similarity of FLS and fibroblasts, including their expression of key fibroblast proteins as well as their mesenchymal origin, it is likely that the effects of artesunate on FLS are largely representative of its effects on *bona fide* fibroblasts[111]. Another report demonstrated that artesunate treatment of FLS at sub-cytotoxic levels concentration-dependently antagonized TNF-α-mediated secretion of proinflammatory cytokines IL-1β, IL-6, and IL-8, and also led to an increase in the secretion of the anti-inflammatory cytokine IL-10. The antagonism of artesunate towards TNF-α-mediated release of proinflammatory cytokines proceeded at least in part *via* artesunate-mediated inhibition of PI3K/Akt and NF-κB signaling[112]. Antagonism of PI3K/Akt and NF-κB in mesenchymal, fibroblast-like cells supports the hypothesis that antagonistic effects of artemisinin compounds in fibrotic diseases may be due to suppression of the inflammatory response in fibroblasts or other myofibroblast precursors through antagonism of PI3K/Akt and/or NF-κB signaling.

In rat alveolar type II epithelial cells, artesunate inhibited TGF-β1-mediated activation of p38, as well as expression of α-SMA and vimentin, suggesting that artesunate treatment can inhibit the EMT[113]. Depending on the organ and the nature of the fibrogenic insult, that inhibition may directly or indirectly, be partly responsible for the decrease in the number of pathological myofibroblasts at the site of fibrotic development, as the EMT may be directly responsible for the accumulation of myofibroblasts in some fibrotic diseases in some tissues114, 115, 116, 117, 118. Similarly, in rat alveolar type II cells, artesunate antagonized TGF-β1-mediated expression of vimentin and α-SMA, indicating suppression of the induction of EMT in alveolar epithelial cells, at least in part through upregulation of the TGF-β signaling inhibitor SMAD7 and subsequent suppression of SMAD3 activation[119].

Treatment of rat glomerular mesangial cells with artesunate inhibited high glucose-induced oxidative stress and expression of extracellular matrix proteins laminin, type IV collagen, and fibronectin. Artesunate also antagonized high glucose-induced activation of the TLR4/NF-κB/NLRP3 inflammasome pathway, suggesting that the protective effects of artesunate operate at least in part *via* inhibition of this pathway[120]. Artesunate also inhibited LPS-mediated proliferation in rat glomerular mesangial cells[121], and DHA inhibited IgA-induced proliferation of human glomerular mesangial cells likely through suppression of mTOR/S6K1 signaling[122]. DHA treatment inhibited proliferation of primary human kidney fibroblasts and TGF-β-mediated fibroblast differentiation, as well as PI3K/Akt signaling, suggesting that DHA-mediated suppression of renal fibrotic development may be due at least in part to antagonism of fibroblast activation *via* suppression of PI3K/Akt signaling downstream of TGF-β[81].

In a rat hepatic stellate cell line, artesunate treatment led to a concentration-dependent decrease in collagen synthesis, suggesting that artesunate can antagonize differentiation of hepatic stellate cells to myofibroblasts and subsequent collagen deposition[103]. In human hepatic stellate cells, artesunate inhibited cellular proliferation, increased cellular ceramide content, and reduced collagen secretion into the media. Artesunate also induced expression of p53, PPARγ, and caspase 3, suggesting that artesunate inhibits hepatic stellate cell proliferation and activation, while promoting the maintenance of stellate cell lipocytic phenotype[123].

In another report using a human hepatic stellate cell line, artesunate concentration-dependently reduced cellular viability *via* induction of apoptosis and reduced expression of transcripts encoding myofibroblast markers α-SMA and type I collagen. Artesunate treatment reduced GSK-3β phosphorylation and downregulated β-catenin, suggesting that artesunate inhibits canonical Wnt signaling, while artesunate also antagonized FAK and Akt activation. Small molecule inhibition of FAK also antagonized Akt activation and Wnt signaling suggesting that, in hepatic stellate cells, artesunate exerts its effects at least in part *via* inhibition of FAK signaling, leading to downstream inhibition of Akt and Wnt/β-catenin signaling[106]. In rat hepatic stellate cells, artesunate antagonized PDGF-BB-mediated release of type I collagen into the culture medium. Artesunate also antagonized PDGF-BB-mediated activation of ERK and expression of cyclin D1, as well as AP-1 DNA-binding activity, suggesting that artesunate inhibits PDGF-BB-mediated stimulation of proliferation and collagen deposition through antagonism of ERK and of subsequent proliferative signaling through AP-1 and cyclin D1[104]. In another report using rat hepatic stellate cells, artesunate reduced cellular proliferation, reduced

the quantity of collagen secreted, and upregulated MMP-13 expression[105]. Taken together, these reports collectively suggest that artemisinin drugs can robustly antagonize myofibroblast activation and downregulate expression of pro-fibrotic genes.

3.3. Anti-angiogenic activity

Some data exist suggesting anti-angiogenic activity of artemisinin drugs, which also may serve to limit development and progression of fibrosis.

In a mouse xenograft tumor model, subcutaneous administration of artesunate resulted in slowed tumor growth, in line with numerous previous reports of artesunate anticancer activity[124], while also reducing the density of blood vessels within the tumor. Tumors in artesunate-treated animals demonstrated lower levels of VEGF compared to tumors in vehicle-treated animals, and artesunate treatment also resulted in reduced expression of VEGFR2 on both tumor cells and endothelial cells throughout the tumor body. Treatment of human umbilical vein endothelial cells (HUVECs) with artesunate resulted in inhibition of proliferation, migration, and aggregation, suggesting that inhibition of tumor angiogenesis by artesunate is at least in part a result of the inhibitory effects of artesunate directly on endothelial cells[125]. In a rat corneal burn model, treatment with eyedrops containing artesunate blunted neovascularization *in vivo*, and artesunate treatment inhibited proliferation and induced apoptosis *in vitro* in HUVECs through Fe^{2+}-mediated generation of ROS and subsequent p38 activation[126]. Artesunate also inhibited proliferation as well as angiogenesis *in vitro* in a matrigel-based assay, demonstrating artesunate-mediated inhibition of endothelial cell proliferation and migration, cellular processes that are critical to the formation of mature blood vessels[127]. Inhibitory effects of artemisinin derivatives on proliferation, viability, and migration of endothelial cells have been detailed in several other reports as well128, 129, 130, 131, 132, 133, 134, 135.

Anti-angiogenic effects were also described in non-endothelial cells that might support angiogenesis through, for example, secretion of pro-angiogenic factors. In FLS derived from human rheumatoid arthritis patients, artesunate decreased hypoxia-induced expression of HIF-1α and secretion of VEGF in a concentration-dependent manner *via* inhibition of PI3K/Akt. These results suggest that artesunate may inhibit angiogenesis by modulating paracrine signaling of non-endothelial cells that act to support angiogenesis[136]. Other evidence suggesting that artemisinin drugs may inhibit angiogenesis through mediation of paracrine signaling exists in reports detailing downregulation of pro-angiogenic factors in various cancer cell lines after treatment with artemisinin derivatives137, 138, 139, 140.

While the direct or indirect anti-angiogenic properties of artesunate may not immediately reveal any obvious mechanism underlying its anti-fibrotic effects, the superfluous, immature angiogenic responses that occur early in the wound healing cascade have been identified as potential targets in order to diminish scarring responses, since previous studies have described comparatively diminished angiogenic bursts observed in the scarless, regenerative wound healing of fetal tissue and of the adult oral mucosa[141]. Further, this relationship appears to be causal in nature, as several reports demonstrate anti-fibrotic results of angiogenesis inhibition *in vivo*142, 143, 144. Thus, it seems plausible to hypothesize that the anti-fibrotic effects of artemisinin derivatives could be due in part to the anti-angiogenic actions of artemisinin compounds initially observed by oncology researchers, but that may also be relevant to the wound environment. The anti-angiogenic effects of artemisinin compounds and their relevance to cancer treatment have been reviewed extensively in Ref. [145]. Taken together, these reports suggest that anti-angiogenic effects may serve as another potential mechanism of action by which artemisinin drugs blunt development of organ fibrosis. A summary of some of the mechanisms by which artemisinins likely prevent or blunt the development of tissue fibrosis by myofibroblast antagonism is presented in Fig. 3.

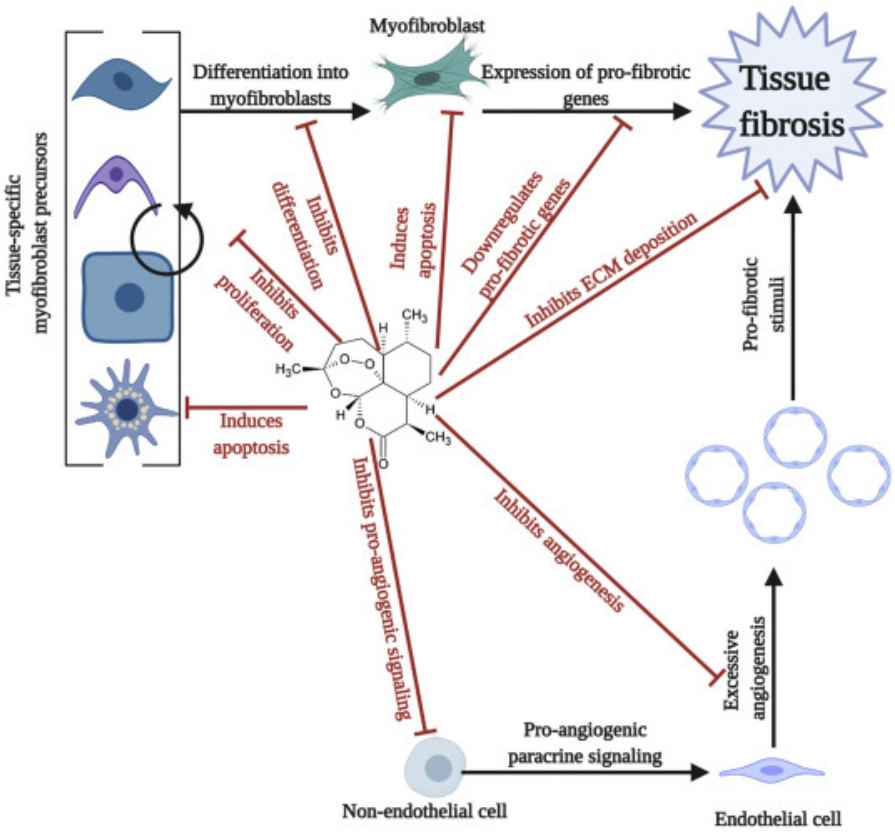

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Figure 3. Potential mechanisms of pharmacologic artemisinin compounds against fibrosis. The effects of artemisinin compounds against pro-fibrotic processes are myriad. Under particular circumstances, artemisinin compounds induce apoptosis, inhibit proliferation, or antagonize differentiation in tissue-specific myofibroblast precursors, preventing accumulation of tissue myofibroblasts that drive tissue fibrosis. In addition, artemisinin compounds antagonize ECM gene expression and downregulate pro-fibrotic genes in myofibroblasts, antagonizing cellular processes that promote accumulation of fibrotic tissue. Further, artemisinin compounds inhibit angiogenesis through direct effects on endothelial cells, as well as through indirect effects *via* downregulation of pro-angiogenic gene expression in angiogenesis-supporting, non-endothelial cells.

4. Potential of whole plant artemisinin to treat internal organ fibrosis

Shared etiologies among multiple types of tissue fibrosis arising in different organs may translate to potential for therapeutic agents to treat multiple fibrotic diseases. For example, the small molecule pirfenidone, which is approved for clinical treatment of idiopathic pulmonary fibrosis in Japan, Europe, and the United States[146], has also demonstrated efficacy towards prevention or reversion of tissue fibrosis in preclinical and/or clinical cases of fibrosis of the liver147, 148, 149, 150, heart151, 152, 153, kidney154, 155, 156 and other organs, as reviewed in Ref. 157. This is unsurprising, as the signaling cascades and cellular effects demonstrated to be modulated by pharmacological pirfenidone both *in vitro* and *in vivo* include pathways ubiquitously implicated in fibrotic diseases such as TGF-β and CCN2/CTGF signaling158, 159, 160, 161. Thus, the pleiotropic effects of artemisinin-based therapeutics observed in pre-clinical animal models and *in vitro*, as described in this review, lend credence to the hypothesis that artemisinin and its chemical derivatives may be useful for the treatment of multiple organ fibroses.

Using artemisinin derivatives as therapeutics for fibrotic diseases, particularly fibrotic diseases affecting internal organs, requires consideration of the physical, chemical, and pharmacokinetic properties of these drugs. Poor solubility

of the artemisinin molecule in oil and in aqueous solutions led to the synthesis of chemical derivatives of artemisinin that show higher solubility in aqueous solutions, including artesunate, or in oil, including artemether[162]. Development of these compounds with different solubility profiles while maintaining the endoperoxide bridge critical to their pharmacological activity enables different drug delivery paradigms to be used in order to deliver artemisinin drugs *in vivo*. Despite successes in total synthesis, semi-synthesis, or microbial production of artemisinin compounds[163], however, the major source of therapeutic artemisinin is still from the *Artemisia* plant[164]. Thus, artemisinin in the *Artemisia* plant may be the most practical and economically viable source of pharmacologic artemisinin for potential treatment diseases, including organ fibrosis[165].

A recent report also analyzed the effects of extracts from three plants from the genus *Artemisia*, *Artemisia capillaris*, *Artemisia iwayomogi*, and *Artemisia annua*, on an immortalized rat hepatic stellate cell line. Extracts from all three *Artemisia* plants demonstrated concentration-dependent inhibition of hepatic stellate cell proliferation and collagen production, as well as inhibited hepatic stellate cell activation *in vitro*[166]. It is important to note that this study used concentrated hot water extracts of *Artemisia* from 100 g dried leaves/per liter, boiled for 150 min then concentrated by rotary evaporation, a process that could have degraded many extracted phytochemicals. Consequently, it was difficult to discern any realistic anti-fibrotic effects of these *Artemisia* extracts on hepatic stellate cells, but the potential remains that phytochemicals could augment the pharmacologic effects of artemisinin towards tissue fibrosis.

Aside from the economic and labor-associated advantages of using *Artemisia* for pharmacologic artemisinin delivery, there appear to be pharmacokinetic advantages as well. In a mouse model, delivery of artemisinin *via* oral consumption of ground leaves of whole plant *A. annua* demonstrated comparable levels of resultant artemisinin drug in blood at a far lower dose compared to oral administration of pure artemisinin delivered in mouse chow (30.7 μg artemisinin in whole plant delivery compared to 1400 μg pure artemisinin in mouse chow), demonstrating that delivery of artemisinin through whole plant oral consumption increased bioavailability compared to oral administration of pure drug[167]. Treatment of a rodent malaria model with orally administered whole plant *A. annua* reduced parasitemia to a greater degree than a comparable dose of pure drug[168]. While the enhanced parasite clearance demonstrated by whole plant therapy compared to pure drug is likely due at least in part to demonstrated cooperative antiparasitic effects of other phytochemicals that constitute the highly complex makeup of *Artemisia* plant tissue169, 170, 171, it is also highly likely that the increased efficacy of whole plant *Artemisia* over pure drug administered orally is due largely to the increased bioavailability of artemisinin specifically. Indeed, simply the presence of plant material (including mouse chow) was sufficient to enable detection of artemisinin in the serum of healthy mice, whereas oral administration of an equal dose of pure drug did not result in a detectable quantity of artemisinin in serum[172]. Simulated digestion experiments have demonstrated that plant matrix and essential oils affect the release and absorption of not only artemisinin but also other bioactive compounds such as flavonoids, suggesting potential mechanisms through which whole plant-derived artemisinin might display greater bioavailability and pharmacologic efficacy *in vivo* compared to pure drug173, 174, 175, 176.

Based on demonstrated greater bioavailability and efficacy, it seems plausible to hypothesize that whole plant *Artemisia* may be an effective strategy to harness the demonstrated efficacy of artemisinin and its chemical analogues for treating organ fibrosis. To understand which fibrotic pathologies might be promising candidates for artemisinin-based therapies, a greater understanding is needed of the nuances, mechanisms, and variability underlying the bioavailability and organ-specific accumulation patterns of artemisinin delivered by different routes of administration and in different forms (*e.g.*, as pure drug, in a capsule, in plant material, etc.).

One very recent report may begin to shed light on the answers to several of these questions. Desrosiers et al.[176] delivered a single oral dose of either a slurry of powdered dried leaf *Artemisia* (DLA) in water, or pure artemisinin drug dissolved in H_2O/DMSO to Sprague–Dawley rats, sacrificed the rats after 1 h, and used gas chromatography/mass spectrometry to determine the amount of artemisinin accumulated across various tissues normalized to the delivered

dose. From this analysis, they concluded that artemisinin delivered orally in the form of DLA was more bioavailable, and thus present in equal or greater amounts, than orally administered pure drug in all tissues examined. In particular, the authors reported differential accumulation of DLA-administered artemisinin, as described by microgram artemisinin per gram of whole tissue, across various tissues. The authors described relatively high accumulation of artemisinin in heart, lung, skeletal muscle, and spleen, moderate accumulation in the liver and brain, and practically no accumulation in the kidney. If these tissue-specific patterns of artemisinin accumulation following DLA ingestion prove to be similar in humans as they are in rats, then these data may shed light on the tissues in which fibrotic diseases might be targetable simply by oral ingestion of *Artemisia* plant material. For example, fibroses of the liver and lungs may be good candidates for further exploration of this treatment modality, as bioaccumulation occurs in these tissues in relatively high amounts, nicely complementing the reports we summarized above demonstrating that artemisinin drugs are effective at blunting tissue fibrosis in these organs in preclinical animal models (refer to Section 2.1. and Section 2.3.). In contrast, the authors report a lack of detectable artemisinin in the kidney suggesting that, despite the varied reports we have summarized above demonstrating blunting of renal fibrosis by administration of artemisinin compounds (refer to Section 2.2.), the treatment modality of oral administration of whole plant *Artemisia* may not be viable for treatment of fibrosis in this tissue. Even in the absence of artemisinin accumulation in renal tissue upon oral administration of DLA, other formulations of artemisinin compounds that can bioaccumulate in the kidney may still hold potential for treatment of renal fibrosis. Additionally, other pharmacokinetic nuances described in the report[176] by Desrosiers et al. may be worth mentioning. The authors noted that artemisinin was completely cleared from serum and from all examined tissues at 8 h post-ingestion, demonstrating that artemisinin had been completely metabolized and/or excreted by this point. Further, larger quantities of artemisinin accumulated in female rats compared to male rats in practically all tissues analyzed, in concordance with a previous report describing more robust first pass metabolism of an i.p.-administered artemisinin emulsion in male rats compared to female rats[177]. If these gender differences hold true in humans, these pharmacokinetic data could be used to guide more precise dosing in individual patients. Last, this report also showed that DLA reduced two LPS-induced inflammation markers, TNF-α and IL-6, to a greater degree than did pure artemisinin. Taken together, this report provides preliminary empirical data to help inform which fibrotic diseases might be good candidates for oral administration of *Artemisia* plant tissue, and which candidates might be better suited for other delivery formulations of artemisinin drugs, or for which artemisinin drugs are unlikely to work more generally. Ongoing and future studies of the drug delivery and pharmacokinetics of *Artemisia* in the form of plant tissue and artemisinin compounds in various pharmaceutical formulations, particularly those performed in humans, will help better assess the potential for artemisinin drugs as anti-fibrotic pharmacological agents.

While a better understanding of the tissue distribution of ingested *Artemisia* in humans will be critical to assessment of the feasibility of this treatment modality to target fibrosis of internal organs, we also believe that published reports describing attenuation of fibrotic phenotypes *in vitro* and *in vivo* by artemisinin compounds in skin compared to those of some other organs[96,97,109], as well as the demonstrated ability of artemisinin compounds to blunt inflammation in varied animal models, lend credence to a proposal for using artemisinin as a topical therapeutic for dermal fibrosis or even other inflammatory skin diseases[112,178, 179, 180, 181, 182], without needing to consider as deeply the pharmacokinetic properties of these drugs. In summary, given all of these reports underlying their efficacy, it seems reasonable to suggest that artemisinin drugs and, perhaps especially DLA, may serve as a promising, cost-effective therapeutic modality for treatment of one or more types of tissue fibrosis.

5. Conclusions

Here we have reviewed many reports demonstrating, we believe convincingly, that artemisinin derivatives attenuate fibrosis in disease models spanning several species and multiple tissues, through various mechanisms largely centering around suppression of pro-fibrotic signaling pathways and prevention of accumulation and persistence of pathological

myofibroblasts. The apparent broad applicability of artemisinin-based therapeutics towards myriad fibrotic diseases is not surprising, given commonalities among pathophysiological mechanisms shared by fibrotic diseases regarding ubiquitous paradigms of activated myofibroblasts, TGF-β signaling, and aberrant regulation of collagen synthesis, maturation, and degradation[3, 4, 5]. We also reviewed reports underlying the demonstration and explanations of the mechanisms underlying heightened bioavailability and pharmacologic efficacy of artemisinin delivered as a whole plant therapeutic or in the presence of plant material compared to artemisinin delivered as a pure drug. We hope that, with a greater understanding of the pharmacokinetic and pharmacodynamic properties of these bioactive agents and the nature of their interactions *in vivo*, artemisinin-based therapeutics for treatment of specific fibrotic diseases may prove efficacious in humans and be used in the clinic.

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Author contributions

David Dolivo conceived of the article, drafted the article, constructed the figures and table, and revised the article. Pamela Weathers and Tanja Dominko provided critical feedback on the conception of the article, as well as on the drafted article itself, and revised the article. All authors reviewed and approved of the final version of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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